REMARKS/ARGUMENTS

Discussion of Claim Amendments

Claim 1 has been amended to recite a method of "reducing" cell death, rather than a method of "inhibiting" cell death, and is supported by the application as filed, *e.g.,* paragraph [0048] and originally filed claims 1 and 11.

Claims 76 and 77 have been amended by the addition of limitations from claim 78, which is canceled.

New claims 79-102 and 104 have been added and are directed to a method of reducing cell death in a mammal using a composition comprising a temporary p53 inhibitor cell protection factor which is supported by the original claims and paragraphs [0050] and [0054]-[0055].

New claim 103 is supported by paragraphs [0054]-[0055].

No new matter has been added by way of these amendments.

The Office Action

The Office Action rejects claims 1, 2, 6, 7, 11-14, 17-20, 23, 25, 27, 29, 31, 33, 35-37, and 76-78 under 35 U.S.C. § 112, first paragraph, for an alleged failure to satisfy the enablement requirement. (Office Action is silent as to claim 75, but for the purposes of this Response Applicants treat it as rejected for lack of enablement). In addition, the Office Action contends that claims 76 and 77 are directed to an invention that is outside of the scope of the claim election made by Applicants in response to the Office's restriction requirement.

Discussion of Rejections Enablement Rejection

Claims 1, 2, 6, 7, 11-14, 17-20, 23, 25, 27, 29, 31, 33, 35-37, and 75-78 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly nonenabled. According to the Office, the specification does not enable a person of skill in the art to make and use the invention commensurate in scope with the rejected claims. Specifically, the Office contends that the specification does not provide enablement because, in part, "[t]he state of the prior art is that the inhibition of cell death *is not an absolute guarantee* in mammals" (emphasis added).

Office Action further contends that there is inadequate enablement because the alleged inability to predict which cell types would avoid cell death results in a requirement for experimentation to determine which cell types would be protected. Office Action also alleges that the application provides only limited guidance as to how to use the invention. The Office Action concludes that the alleged lack of predictability and guidance combine to result in a requirement for an undue amount of experimentation to practice the claims' alleged broad scope. The Office Action reaches this conclusion despite acknowledging that there is the high level of skill in the art. Applicants respectfully submit that even before the instant amendments, but certainly in view of them, the Office Action is mistaken with respect to any alleged failure to enable the invention.

First, an enabling disclosure does not have to provide *an absolute guarantee* of success, nor must the prior art provide such a guarantee. The scope of the required enablement merely varies inversely with the degree of predictability the art involved. *In re Fisher*, 427 F.2d 833, 839, 166 U.S.P.Q 18, 24 (C.C.P.A. 1970). Additionally, the presence of working examples and a high level of skill in the art weigh in favor the presence of an enabling disclosure. *In re Wands*, 8 U.S.P.Q.2d 1400, 1406 (Fed. Cir. 1988). Moreover, even in unpredictable arts, a disclosure of every possible operable species is not required. *In re Vickers*, 141 F.2d 522, 526-27, 61 U.S.P.Q. 122, 127 (C.C.P.A. 1944); *In re Cook*, 439 F.2d 730, 734, 169 U.S.P.Q. 298, 301 (C.C.P.A. 1971).

Moreover, the art with respect to the use of cell protection factors for inhibiting cell death, is reasonably predictable. A routine PubMed or Google search for "cell protection factors" or "cell death inhibitors," for example, provides an enormous number of inhibitors, including p35, Bcl inhibitors, and pifithrin (see also the specification at paragraph [0049]). The teachings of the prior art, with respect to bone targeting agents and cleavable linkers, are such that the claimed invention can be made and used with a reasonable degree of predictabiility. PubMed or Google searches for both "bone targeting agents" and "cleavable linkages" provide numerous examples. Thus, in view of the acknowledged high level of skill in the art and based on the extensive collection of prior art references relating to cell protection factors, bone targeting agents, and linkers, Applicants respectfully submit those of ordinary skill in the art can, without undue experimentation, make and use the invention and, thus, that the specification is enabling.

Applicants also submit that the specification provides substantial guidance to those of ordinary skill in the art. Examples 1 and 17-71 provide guidance as to how to make numerous exemplary cell protection factors. Paragraphs [0072]-[0076] teach a variety of bone marrow targeting agents and paragraphs [0071] and Example 4 teaches how to choose a suitable bone marrow targeting agent. Paragraphs [0079]-[0093] teach suitable linkers and Examples 2, 3, 5 teach how to use linkers in accordance with the invention. Paragraph [0054] teaches how to measure apoptosis and Examples 6 and 7 teach methods of evaluating the reversibility of the inventive compounds effects, methods of verifying the bone affinity, and methods of evaluating the p53-inhibitory activity of a cell protection factor upon release from of a cell protection factor-linker-bone targeting agent complex. Specifically, considering the instant claim amendments, these sections clearly offer extensive guidance relating to temporary p53 inhibition and to bone marrow protection.

Applicants also submit that, in view nature of the art, it can not reasonably be said that an "undue amount of experimentation" is needed to practice the full scope of the claims. A patent application need not be a production protocol. *In re Gray*, 135 U.S.P.Q. 311 (C.C.P.A. 1962). What constitutes "undue" experimentation depends on the field. Automated high-throughput screening is widely used in the pharmaceutical arts. The specification teaches methods which identify which compounds that inhibit apoptosis (e.g. Example 7, paragraph [0139], "TUNEL'), and, in particular, which compounds would inhibit p53 mediated apoptosis using high throughput screens (see, e.g., paragraphs [0137]-[0138]).

Applicants further submit that, in view of the instant amendments, it can no longer reasonably be said that the claims have an "extremely broad scope." The instant amendments only enhance Applicants' position that enablement commensurate with the claim scope is present. As amended herein, claims 1-75 are now directed to reducing cell death in bone marrow cells and, thus, a smaller number of types or classes of cells is now claimed.

Enablement is a dynamic inquiry and the state of the prior art in apoptosis and cancer biology should be assessed at the time the application was filed. *Chiron Corp. v. Genentech Inc.*, 363 F.3d 1247, 1254, 70 U.S.P.Q.2d 1321, 1325-26 (Fed. Cir. 2004). By the time the priority parent application (U.S. Appl. No. 60/460,289) was filed in April 2003, there was an extensive prior art relating to the isolation and use of cell protection factors. As amended the claims are directed to the use of cell protection factors, an example of which is a temporary

p53 inhibitor. At the time the application was filed, p53 was well-known as an *ubiquitously* expressed apoptosis control protein (*see, e.g., Oncogene* (2002) 21, 6722 - 6728, Abstract (Exhibit 1); *Microbiology and Molecular Biology Reviews*, (June 2002) 66 179–202; 163, "p53" section's 3rd paragraph (Exhibit 2); *Clinical Cancer Research* (February 2002) 8, 494–501, 499, column 2, paragraph 2 (Exhibit 3)). Accordingly, a temporary p53 inhibitor could readily be predicted to reduce apoptosis in *all* types or classes of cells.

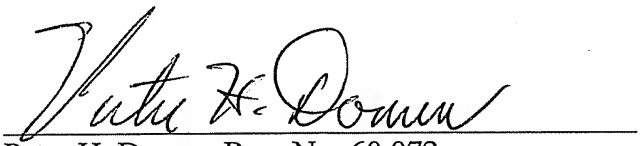
Moreover, in embodiments Applicants claim a method wherein a well-known p53 inhibitor is delivered close to the location of the bone marrow through the use of a targeting agent covalently bonded to a polymer. Such focused delivery of the inhibitor in fact should increase the degree of predictability of the claimed method.

In view of the foregoing, Applicants respectfully submit that the skilled artisan, considering the current disclosure and the state of the art, would be able to make and use the method of claims as instantly amended without undue experimentation. Based on the foregoing, Applicants respectfully request that the lack of enablement rejection be withdrawn.

Conclusion

Applicants respectfully submit that the patent application is in condition for allowance. If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned attorney.

Respectfully submitted,



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Date: August 20, 2007